page 28, Table 5, after the fourth line of text at the bottom of the table ending "the pertussis toxin gene (PTX). E. coli", insert the following which was indicated by the Examiner to be illegible

--usage based on 5253 codons for highly expressed genes (S) and 5231 codons for moderate to weakly expressed genes (W).
[d]ND not determined--.

In the claims:

claim 5, line 1, delete "at least"; and

at line 3, change both occurrences of the word "portion" to --toxin--; and

at line 4, delete "capable of".

claim 8, line 2, change "15" to --14--.

Remarks

The Office Action requested that the status of all related applications should be indicated at the beginning of the specification. This information was submitted as a Preliminary Amendment incorporated with the filing papers. See attached Appendix A. In the event, the preliminary amendment instructions on this filing paper can not be executed at this time, please notify applicant's agent and a new amendment therefor will be submitted.

The specification and claims have been amended according to the kind suggestions of the Examiner. The material amended at the end of Table 5 corresponds to the text in parent application 07/311,612, as required of filings under 37 CFR 1.60. The

amendment of claim 8 corrects an inadvertent error. The actual fragments used in the cloning work extended from Tyr 8 to Pro 14; rather than Pro 15. Page 44 of the specification details the cloning procedure involving excision and ligation of homology box fragments extending from Tyr 8 through Pro 14. Consequently, no new matter has been introduced by the above amendments.

Rejections under 35 U.S.C. 112, Second Paragraph

On page 4 of the 06/19/91 Office Action, the Examiner criticized several terms in claim 5 as being indefinite, and consequently, rejected claims 5-10 under 35 U.S.C. 112, second paragraph. This set of rejections is traversed.

The Examiner questioned how much of the claimed cloned gene constitutes "at least a portion" encoding a mutant B. pertussis toxin. While the exact nature of the Examiner's confusion regarding this phrase is not clear, it appears to revolve around the use of "at least" in conjunction with "a portion". To advance prosecution, the phrase "at least" has been deleted. The Examiner went on to speculate that a dipeptide would apparently have sufficed. A dipeptide, as well as any other sized peptide/polypeptide, would be within the scope of what applicant considers his invention; provided it possessed all the other limitations of the claim. Namely, such peptide/polypeptide must be a mutant B. pertussis toxin, or a fragment or a derivative of said toxin; it must comprise a epitope contributing to immunoprotection against pertussis toxicity; and it must have substantially reduced

enzymatic activity associated with pertussis toxin reactogenicity. Claim 5 has also been amended to more precisely indicate that the "fragment" or "derivative" refers to the toxin. The examiner also questioned which derivative has an epitope conferring immunoprotection. The scope of claim 5 encompasses all derivatives of the toxin having such an epitope, as well as the other required limitations of the claim. Claims 6-10, however, limit such derivatives to all derivatives of exotoxin subunit S1 which possess the required attributes.

The Examiner objected to the claim terminology "capable of". Following the Examiner's kind suggestion, this phrase has been deleted from the claims.

The Examiner noted that the claims were subject to the "alternative" interpretation that includes any protein that provides the immunogenic function. It is not clear to applicant what other interpretation the Examiner had in mind. As indicated, supra, the Examiner correctly interprets the claims, provided the protein expressed from the cloned gene possesses also all the other limitations of the instant claims.

The phrase "substantially reduced" was criticized; with the Examiner expressing apparent confusion as to how much enzymatic activity corresponds to "substantially reduced". The Examiner then queried whether substantially reduced enzyme activity corresponded to 1/2 or 0.00000001%. Firstly, the Examiner is directed to page 47, lines 10-13, wherein the meaning of the term "substantially reduced" enzyme activity is disclosed. Secondly, the CCPA has

determined that Section 112, second paragraph rejections based on a fact pattern analogous to this is not proper. In In re Mattison and Swanson, 184 USPQ 484 (CCPA 1975), the court ruled on an indefiniteness criticism of the analogous term "substantially increase". In its earlier opinion, the Patent Office Board of Appeals asked the analogous question,

> How much is a substantial increase? Is it 3%, 30%, 300%, or something else? Since the answer to this question must be known in order to determine whether a particular compound is or is not within the scope of the subject matter claimed, we hold that the claims are indefinite and accordingly affirm the rejection based on the second paragraph of 35 U.S.C. 112.

On page 486 of the CCPA decision on appeal, Judge Baldwin stated:

> Hypothesizing whether an increase in efficiency of 3%, 30%, or 300% is necessary for said increase to be classified as substantial is not determinative of the issue of whether the claims satisfy 35 U.S.C. 112, second paragraph.

Finally, the examiner questioned the meaning of the term "reactogenicity", and indicated that it did not appear to have antecedent basis in the specification. Reactogenicity is a term of the art in the field of vaccine development. It refers to pathophysiological activities or reactions associated with a vaccine. In the instant invention, the ADP-ribosyltransferase enzyme activity of the S1 subunit of pertussis toxin causes reactogenetic responses associated with neurological damage (e.g., convulsions and encephalopathy). See the description on page 2 of the specification. Indeed, it is an object of the instant invention to eliminate such reactogenicity, while maintaining the

protective immunogenic properties of the toxin (See page 6, lines 2-16). Evidence for the common use of this term of art and its specific use in reference to the enzymatic activities associated with pertussis toxic can be found in the art of record. See the 1988 Burnette et al reference cited against all the instant claims. Also, see the specification and claims of the European Patent Application made of record in the last Office Action. It is well established that definiteness of language employed in claims must be analyzed in light of teachings of prior art and of the particular application disclosure as it would be interpreted by one possessing ordinary level of skill in the pertinent art. Claims may appear indefinite when read in a vacuum, but may be definite upon reading of specification or prior art teachings. In re Moore and Janoski, 169 USPQ 236 (CCPA 1971).

Regarding the criticism that there is no apparent antecedent basis for reactogenicity, the Examiner is reminded that the claimed subject matter need not be described in haec verba in the specification in order for the specification to satisfy the description requirement. In re Wright, 9 USPQ2d 1649 (Fed Cir 1989). Also, see the CCPA decision in re Anderson, 176 USPQ 331 (CCPA 1973), wherein the court indicated that in determining whether an amendment to claims constitute new matter, the question is not whether added word was a word used in the specification as filed, but whether there is support in specification for employment of word in claim, i.e., whether concept is present in original disclosure. In the instant fact situation, applicant's use of the

term "reactogenicity" is consistent with and in concert with its art-recognized use, and the specification has ample support for the concept of pertussis toxin proteins with reactinogenic properties.

For all the above reasons, it is respectfully submitted that the claims, as amended, are definite and distinct, and the Examiner is requested to withdraw the criticisms under 35 U.S.C. 112, second paragraph.

Rejections under 35 U.S.C. 102 and 103

On page 5 of the 06/19/91 Office Action, all the pending claims were rejected under 35 U.S.C. 102(a) as being clearly anticipated by Burnette et al. (Science). The Examiner's attention is drawn to the attached Declaration, by applicant, submitted under 37 CFR 1.131. This declaration provides evidence of applicant's conception and reduction to practice of the claimed invention, in the United States, prior to the publication of the above identified reference. Consequently, Burnette et al (Science) is not art against the instant claims, and the Examiner is respectfully requested to withdrawn this rejection.

On pages 5-6 of the 06/19/91 Office Action, all the claims were rejected under 35 U.S.C. 102(b) as anticipated, or in the alternative, under 35 U.S.C. 103 as obvious over Burnette et al (J. Cell Biochem). This rejection is traversed. Proper evaluation of the 102/103 rejection asserted by the Examiner requires analysis of several considerations not fully developed or made clear in the Office Action.

One consideration is if the Burnette reference is sufficiently enabling to anticipate each element of applicant's claimed invention. The law is clear that before a publication can be an anticipating bar to the grant of a patent, its disclosure must be such that the skilled artisan could take its teachings in combination with his own knowledge of the particular art and be **in possession of the claimed invention**. In re LeGrice, 133 USPQ 365 (CCPA 1962). To satisfy the broadest aspect of applicant's claimed invention, the Burnette reference must place into the possession of the public a cloned gene encoding a protein having immunoprotective properties but substantially reduced enzyme activity. By contrast, all the pertussis toxin constructs described in the Burnette reference (including the tyrosine 8 to proline 14 construct) exhibit both enzymatic and immunoprotective functions. Consequently, no construct actually disclosed in the reference satisfies all the limitations of even the broadest claimed invention. Needless to say, the Burnette reference neither discloses nor suggests the specific change of arginine 9 to lysine required in claim 10.

The Examiner noted the specific Tyrosine 8 to proline 14 construct of Burnette, and then began, under open quotation marks, the following direct quote from the reference: "more precise mapping was accomplished by producing a progressive series of amino-terminally truncated recombinant proteins... Without ever closing quotation marks, the Examiner continued the above sentence with his own extrapolated conclusion, which read;--where the test

set forth would reasonably have determined the activity profile of the deletion mutations. It appears the Examiner is alleging that the truncation procedure was being applied further to the Tyr 8 to Pro 14 peptide. This is never recited or suggested in the reference. Rather, the truncation and more precise mapping passage relates to work done on larger deletion fragments of the S1 subunit of pertussis toxin culminating in the Tyr 8 to Pro 14 peptide. There is no suggestion from the reference that further application/extension of this truncation procedure should be pursued to make smaller peptides; or that such extrapolation could reasonably be expected to place into the possession of the public smaller peptides which are devoid of enzyme activity; yet retain protective immunogenicity.

Even assuming arguendo that such truncation procedures were applied to the Tyr 8 to Pro 14 fragment of Burnette to produce a peptide with substantially reduced enzyme activity and retained immuogenicity, this peptide would not read on instant claims 8-10. Claims 8-10 require the peptide to have a site-specific mutation in the region bounded by tyrosine 8 and proline 14 (i.e., a required heptapeptide configuration). Additional truncation of this peptide necessarily creates a peptide region smaller than this required heptapeptide, and thus could not satisfy the required claim limitation of a region bounded by Tyr 8 and Pro 14. Furthermore, the Examiner's proposed extrapolation of the amino-terminal truncation process in Burnett physically could not produce the invention of claim 10. Claim 10 requires a specific amino acid

change of arginine 9 to lysine. The truncation procedure of Burnette does not change one amino acid to another; rather it merely causes deletion of amino acids.

The Examiner followed the above anticipation argument with the following passage:

> and where in the alternative, the application of art recognized processes such as site directed mutagenesis would have resulted in DNA coding for any amino acid substitution at any of positions 8-14 where only routine testing as indicated in the reference would have been needed to determine the enzymatic and immunogenic characteristics coded for by that modified DNA which coded for the least enzymatic S1 pertussis toxin that retained the appropriate epitope specificity.

It is assumed this constituted the basis for the alternative obviousness rejection of the claims. Indeed, art-recognized processes such as site directed mutagenesis could conceivably create any amino acid substitution at any of positions 8-14 in the peptide construction of Burnette. This, of course, encompasses 140 different mutation events corresponding to the 20 possible amino acid substitutions at each of the 7 positions of Tyr 8 to Pro 14. However, it is only through hindsight knowledge of applicant's invention that one would know that a single amino acid change would be sufficient. Without that hindsight guidance, the person of ordinary skill in this art also would have to systematically test every possible two, three, four, five, six, and seven amino acid set of mutation permutations, wherein again each amino acid could be any one of 20 possibilities. Without belaboring the exponential statistics involved, the experimental design permutations facing

the person of ordinary skill embarking upon this endeavor are astronomical. It is appreciated that one can not ignore the broader, instructive disclosure of a reference which teaches how to modify exemplary compositions. However, it is also well established that there can be no anticipation of an invention where the reference is so broad that the likelihood of arriving at the claimed composition would be the same as discovering the combination of a safe by an inspection of the numbers on the dial. Ex parte Garvey, 41 USPQ 583 (POBA 1939) and Ex parte Starr 44 USPQ 545 (POBA 1938).

Similar considerations apply when determining whether a reference renders an invention obvious or merely obvious to try. The CAFC in In re O'Farrell, 7 USPQ2d 1673 (Fed Cir. 1988) set forth criteria to distinguish when the obviousness of an invention is determined using an impermissible "obvious to try" standard. One such situation delineated by the court is when the skilled artisan must try each of numerous possible choices until one possibly arrives at a successful result, where the prior art gives no direction as to which of many possible choices is likely to be successful. It is submitted that the above criterion identifying an "obvious to try" scenario perfectly fits the fact situation in the present art reject.

Another consideration, bearing on the instant art rejections, that was not adequately or completely addressed in 06/19/91 Office Action is the matter of priority date benefit under 35 U.S.C. 120. On page 7 of the instant Office Action, the Examiner indicated that

newly added material starting at Example 1 on page 43, related specifically to the genetic mutations, is not afforded priority date benefit of grandparent application 06/843,727 (Patent 4,883,761). However, the Examiner failed to identify which pending claims rely on the new matter (effective filing date of 02/15/89), and which do not so rely and deserve priority benefit back to 03/25/86. It is respectfully submitted that instant claims 5-7 should be afforded priority benefit and have an effective filing date of 03/25/86. The original 06/843,727 application disclosed cloning immunoprotective pertussis toxin subunits, including the S1 subunit, for use in developing safer, less toxic vaccines for whooping cough. The '761 patent at column 23, line 23 to column 24, line 5 states:

> The cloned and sequenced pertussis toxin genes are useful for the development of an efficient and safer vaccine against whooping cough. By comparison to other toxin genes with similar biochemical functions and by physical identification of the active sites either for the ADP-ribosylation in the S1 subunit or the target cell binding in subunits S2 through S4, it is now possible to modify those sites by site-directed mutagenesis of the B. pertussis genome. These modifications could abolish the pathobiological activities of pertussis toxin without hampering its immunogenicity and protectivity.

It is respectfully submitted that this disclosure is at least as enabling, regarding the application of site-directed mutagenesis, as the disclosure relied upon in the Burnette (Journ. Cell. Biochem) reference which merely states,

> These studies will permit use to construct recombinant site-specific S1 mutants that retain an important protective epitope, yet

eliminate enzyme-related reactogenicity.

The Examiner feels the above Burnette disclosure, supplemented by only routine testing/experimentation, is sufficent to place the claimed invention into the hands of the public (i.e., make the invention), and, thereby, render the invention obvious. Consistency dictates the Examiner reach the same conclusion regarding the sufficiency of the analogous original disclosure in the '727 application relative to instant generic claims 5-7. Pending claims 5-7 do not rely upon the specific new matter disclosure of parent CIP 07/311,612 related to the Tyr 8 to Pro 14 region or the specific replacement of Arg 9 with lysine. The Examiner is respectfully requested to indicate the effective filing date of claims 5-7 to be 03/25/86. This effective filing date is prior to the publication date of the Burnette (Journ. Cell Biochem) reference and, therefore, removes this reference as prior art against claims 5-7. The Examiner is respectfully requested to declare claims 5-7 to be free of the art.

One additional consideration bears upon the determination of obviousness of the instant claims over the Burnette reference. This relates to serious negative teachings in the art which would mitigate against the person of ordinary skill in this art being motivated to try genetically modifying the S1 subunit of pertussis toxin to fashion a vaccine with immunoprotective properties but substantially reduced enzyme activity.

The Examiner is directed to the attached Black et al reference published after the Burnette reference, but before the filing date

of parent CIP application '612. Black et al investigated the relationship between ADP-ribosyltransferase activity of pertussis toxin and the immunoprotective capacity of the toxin. Black et al found a direct correlation between these two functions. In the last paragraph of the article, the authors summarize these findings and declare:

> These data imply that mutations in the toxin genes that reduce pathogenic activities of a strain such as leukocytosis can also reduce immunoprotective capacity of the strain. This is an important consideratiion in the formulation of future pertussis vaccines.

The Examiner is directed also to the attached Cieplak et al reference published by PNAS in July 1988. This article represents the full manuscript version of the Burnette (Journ Cell.Biochem) Abstract reference applied against the instant claims. Please be directed to the last paragraph on page 4670, wherein the same authors as the Burnette Abstract reference, analyzing in greater detail the same experimental evidence regarding the Tyr 8 to Pro 14 homology box disclosed in the Burnette Abstract reference reach the conclusion that:

> The epitope for monoclonal antibody 1B7 resides, either entirely or in part, within the homology box. This finding suggests that removal of this box to eliminate enzymatic activity of PTX could have the unwanted effect of reducing or even eliminating, its protective immunogenicity.

This disclosure reinforces the Black et al warning indicated, supra. These combined warnings represent strong negative teachings in the art to a skilled artisan contemplating making genetic changes to the homology box for the purpose of eliminating enzyme

activity while retaining immunoprotective function. On the other hand, applicant's success in creating these kind of genetic mutants in the face of such negative teachings in the art is objective evidence of non-obviousness. Where, as here, the art strongly teaches against the approach successfully pursued by applicant, this secondary consideration of non-obviousness can be determinative of patentability.

The Cieplak et al reference is an intermediate citation published after the earliest priority date and less than one year before the 02/15/89 priority date of CIP 07/311,612. To advance prosecution, and eliminate this reference being applied against the claims under 35 U.S.C. 102(a)/103, the attached 131 Declaration evidences conception and reduction to practice of the instant invention prior to the July 1988 publication date of this reference.

On page 6 of the instant Office Action, claims 5-10 are rejected as obvious over Locht et al in view of Burnette (J. Cell. Biochem). This art rejection is traversed. Locht is the journal version of the disclosure set forth in the original grandparent application 06/843,727. This article is referenced in the Burnette abstract article, and contributes nothing more than background art for the instant invention. If the later derivative work encompassed by the Burnette reference does not anticipate or render obvious the claimed invention for reasons set forth, supra, then combination with its antecedent first teachings reference does not advance the

Examiner's lack of a Prima Facie case. For all the reasons enumerated previously, this combination of art does not render the instant claims obvious.

The Office Action of 06/19/91 sets forth obvious-type double patenting rejections of all the claims over claim 1 of the 4,883,761 patent in view of the two Burnette et al references. As indicated previously, the Burnette (Science) article has been removed as available prior art. The relationship between the patent claim and Burnette (J. Cell. Biochem) is analogous to the combination with Locht et al, supra. Patent claim 1 contributes nothing more to the obviousness determination than is already present in the Burnette reference. If the Burnette reference is not sufficient to render the claims obvious for all the reasons set forth above, combination with claim 1 of the patent does not cure any deficiencies or advance the prima facie case. If the Office believes the Burnette reference anticipates or renders obvious applicant's claimed invention, the rejection of the instant claims on those grounds should be pursued on its merits. If the Burnette reference does not anticipate or establish a prima facie case on its own merits, it seems improper and unfair to attempt to use that same reference in an independently restrictive manner to reduce the patent term of a novel and unobvious invention.

All claims are believed to be in condition for allowance, and notification to this effect is earnestly requested. In the event the Examiner feels a personal interview would advance prosecution of this application, please contact applicants' attorney at the

telephone number indicated below.

Respectfully submitted,

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